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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/887,496	06/22/2001	Partha S. Banerjee	18025-1014	7707

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EXAMINER	
KANTAMNENI, SHOBHA	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 07/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/887,496	BANERJEE ET AL.	
	Examiner	Art Unit	
	Shobha Kantamneni	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21,23-38,40-64,69-76,78-83,87-89,93 and 99-122* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *NONE* is/are allowed.

6)☒ Claim(s) *1,3-21,23-38,40-64,69-76,78-83,87-89,93 and 99-122* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *01/13/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 01/13/2006 has been entered.

Applicant's amendment filed on 01/13/2006 wherein independent claims 1, 78, 87-89 have been amended, and claims 2, and 77 have been canceled. A new claim 122 has been added.

Currently, claims 1-21, 23-38, 40-64, 65-68, 69-76, 78-83, 87-89, 93, and 99-121 are pending in this application.

It is noted that claims 65-68 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claims 1, 3-21, 23-38, 40-64, 69-76, 78-83, 87-89, 93 and 99-122 are examined on the merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 87-89 are rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification, while being enabling for the treatment or amelioration of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction disclosed in the specification employing the combination herein, does not reasonably provide enablement for the prevention of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction recited in these claims.

The instant claims are drawn to an article of manufacture for the prevention of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction. The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention. Attention is directed to In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the ad; (4) the predictability or unpredictability of the ad; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples', and (8) the quantity of experimentation necessary.

Nature of the invention: The instant invention pertains to an article of manufacture for the prevention of one or more symptoms of diseases or disorders

associated with undesired and/or uncontrolled bronchoconstriction in a human or animal.

The state of the prior art: The skilled artisan would view that the prevention of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction in a human or animal totally, absolutely, or permanently. is highly unlikely, not even occurring at the first time.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or lack thereof in the art: The skilled artisan would view that the treatment to prevent one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction in a human or animal totally, absolutely, or permanently is highly unpredictable, and not even occur at the first time is highly unpredictable.

The amount of direction or guidance presented and the presence or absence of working examples: In the instant case, no working examples are presented in the specification as filed showing how to prevent one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction in a human or animal totally, absolutely, or permanently, not even occurring at the first time. Note that lack of a working example, is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP 2164. Note that Applicant also admits that bronchoconstriction in a human or animal is "uncontrolled".

Genentech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and [p]latent

protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors, e.g., the amount of direction or guidance provided, absence of working examples, and the predictability of the art discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test the combination in the instant claims whether preventing one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction in a human or animal totally, absolutely, or permanently, with no assurance of success.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-21, 23-38, 40-64, 73-76, 78-83, 87-89, 99-112, 117-119, and 122 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hochrainner et al. (US 6,150,418, PTO-892 of record) in view of Blondino et al. (US 6,004,537, PTO-892 of record) or Carling et al. (US 5674860, PTO-892 of record).

Hochrainner et al. discloses propellant-free pharmaceutical composition comprising formoterol particularly stable on storage with concentration 10 –500 mg/ml

(see col.1 line 65-67; col.2 line 6-11), in aqueous ethanol, and ethanol mixture (water and ethanol are well known polar and protic solvents, see col.2 lines 24-34), in the form of a solution or suspension for use in inhalers for nasal therapy, see abstract and claims 1-4 in particular. Hochrainer et al. further teaches that the pharmaceutical composition is such that it can be administered by inhalation using a suitable nebuliser, see col.4, lines 19-20 and col. 5, lines 33-41. Hochrainer et al. teaches that the pH range is preferably between 2.0-7.0 and most preferably between 4.5-5.5. The employment of inorganic acids and organic acids such as phosphoric acids, citric acid and the employment of buffers in its composition are also taught, see in particular col.3, lines 35-40 and col.4 line 55 to col. 5, line 7; and inorganic salts, sodium chloride, and organic salts such as for example, sodium, potassium or ammonium salts of citric acid (see col.2 lines 56-64) in the composition is also taught. Hochrainer et al. teaches the concentration of formoterol to be between about 75 mg/ml and about 500 mg/ml, which may be used with diluent, and other ingredients for the preparation of therapeutical composition. See in particular claims 1-4. Hochrainer et al. also teaches that additional active ingredients such as steroids, antichlolinergics could be incorporated in its composition, see claim 19. It is taught that the formulation for administration is obtained by diluting to 0.9 mg/ml of formoterol with the diluents such as water, aqueous saline and the PH is adjusted for stable storage. See column 4, lines 26-29; column 5, lines 1-6. Hochrainer et al. also discloses a kit or an article of manufacture comprising the same combination and a nebulizer. See column 5, lines 33-47. The compositions therein are employed in the methods of treating obstructive respiratory diseases and

asthma, see col. 1, lines 1- 37. A formulation containing a solvent mixture of ethanol/water, formoterol in a concentration of about 0.9 to about 1.5 mg/ml adjusted to a pH of about 4.5 to about 5.5 is also disclosed. See column 8, claim 22.

Hochrainer et al. does not teach particularly the employment of a steroidal anti-inflammatory agent, budesonide or fluticasone propionate.

Hochrainer et al. does not explicitly teach the concentration of formoterol such as 50 μg/ml to about 200 μg/ml, 59 μg/ml, 118 μg/ml in its pharmaceutical composition, and does not expressly teach the concentration of buffer providing particular PH value, and the ionic strength of the composition.

Blondino et al. discloses a pharmaceutical composition comprising formoterol (free base) or formoterol fumarate salt in combination with the specific steroid anti-inflammatory agent, budesonide (see col.2 lines 9-25), in a pharmaceutically acceptable carrier such as a liquid, co-solvents of alcohols such as ethanol or isopropanol (see col.2 line 55-59), by inhalation from a nebulizer for treatment (see title and abstract, claims 1-30). Blondino et al. also discloses the effective amounts of formoterol, in amount 0.01-0.5% by weight in a pharmaceutical composition therein (see claim 1). Blondino et al. also discloses that the composition or formulation therein is stable under elevated temperatures, e.g., 45^0C (see col.2 lines 35-37). Blondino et al. also discloses that a pharmaceutical composition of the combination therein is formulated into a single dosage administration (see Example 1-4 at col.4). Blondino et al. also discloses a kit or an article of manufacture comprising the same combination and a inhaler (see col.3-4, claims 1-30).

Carling et al. discloses a pharmaceutical composition comprising formoterol (free base) or formoterol fumarate salt in combination with the specific steroid anti-inflammatory agent, budesonide, in a pharmaceutically acceptable fluid such as a liquid (see col.4 line 2), by inhalation from a nebulizer (see col.3 line 51) for the treatment of respiratory disorders such as asthma (see title and abstract, col.1 lines 10-15, 46-67). Carling et al. also discloses the effective amount of formoterol, 6-100 μg, preferred 6-48 μg (the instant claimed amount within the range of Carling et al.), in a pharmaceutical composition therein (see col.3 lines 44-45). Carling et al. also discloses that a pharmaceutical composition of the combination therein is formulated into a single dosage administration (see Example 1-3 at col.4). Carling et al. also discloses a kit or an article of manufacture comprising the same combination and a nebulizer (see col.3 line 8-10 and 50-52, claims 1-36). Carling et al. also discloses the employment of a tonicity adjusting agent herein such as salts of inorganic or organic salts, e.g., succinate, lactate (see col.3 lines 30-38) and adding oleic acid may improve the physical stability (see col.4 line 12-14).

From the teaching of Carling et al. or Blondino et al., it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ budesonide in the composition of Hochrainer et al. It is prima facie obvious to combine two agents which are known to be useful to treat asthma individually into a single composition useful for the very same purpose. See *In re Kerkhoven* 205 USPQ 1069.

It would have been obvious to a person of ordinary skill in the art at the time of invention to optimize parameters such as the concentration of formoterol in its

pharmaceutical composition, and the concentration of buffer providing particular PH value, and the ionic strength of the composition. The optimization of a result effective parameter, e.g., the effective amounts of active ingredients and excipients in a therapeutical dosage form, is considered within the skill of the artisan. See, In re Boesch and Slanev (CCPA) 204 USPQ 215.

With regard to the limitations "whereby the composition has an estimated shelf-life of greater than 1 month usage time at 25 °C and greater than or equal to 1 year storage time at 5 °C, and "the composition is formulated for direct administration", Hochrainer et al. disclose a formulation containing a solvent mixture of ethanol/water, formoterol in a concentration of about 0.9 to about 1.5 mg/ml adjusted to a pH of about 4.5 to about 5.5, and further teaches that the compositions therein are obtained by diluting with polar solvents such as water, aqueous saline and adjusting the PH to obtain a stable formlation. See column 8, claim 22. Hochrainer et al. particularly teach that the concentrated solution may be used for making pharmaceutical composition which is such that it can be administered by inhalation using a suitable nebuliser, see col. 4, lines 19-20 and col. 5, lines 33-41. The compositions therein can contain steroids. Thus, absent showing unexpected, and significant benefit residing in the particular limitation herein, the claimed invention would have been obvious to one of skill in the art.

Claims 69-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hochrainner et al. (US 6150418, PTO-892 of record) in view of Carling et al. (US

5674860, PTO-892 of record) or Blondino et al. as applied to claims 1, 3-21, 23-38, 40-64, 73-76, 78-83, 87-89, 99-112,117-119, and 122 and further in view of PDR.

Hochrainner et al., Carling et al. and Blondino et al. are as discussed above.

The prior art combination of references does not teach particularly the employment of a steroidal anti-inflammatory agent, fluticasone propionate or its concentration.

PDR teaches fluticasone propionate as a known corticosteroid readily employed in the method of treating asthma.

From the teaching of PDR, it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ fluticasone propionate in the composition of Hochrainer et al. It is prima facie obvious to combine two agents which are known to be useful to treat asthma individually into a single composition useful for the very same purpose is prima facie obvious. See *In re Kerkhoven* 205 USPQ 1069.

The optimization of a result effective parameter, e.g., the effective amounts of active ingredients and excipients in a therapeutical dosage form, is considered within the skill of the artisan. See, In re Boesch and Slanev (CCPA) 204 USPQ 215.

Claim 93 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hochrainner et al. (US 6150418, PTO-892 of record) in view of Blondino et al. (US 6004537, PTO-892 of record) or Carling et al. (US 5674860, PTO-892 of record), and further in view of PDR at pages 482, 535, 537, 2828 (of record).

The same disclosures of Hochrainner et al. in view Carling et al. (US 5674860) or Blondino et al. have been discussed in the 103(a) rejection set forth above.

Hochrainner et al., Carling et al. and Blondino et al. do not expressly disclose further adding one or more agent recited in claim 93 herein to the composition.

PDR teaches that albuterol (beta2-adrenoreceptor agonist), accolate (leukotriene receptor antagonist) and Zyflo (5-lipoxygenase inhibitor) are all known to be effective in treating asthma.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ a third active such as those enumerated immediately above in a combination composition along with formoterol and budesonide.

One of ordinary skill in the art would have been motivated to employ a third active such as those enumerated immediately above in a combination composition along with formoterol and budesonide because all three actives are known to be useful in treating asthma. Combining two agents which are known to be useful to treat asthma individually into a single composition useful for the very same purpose is prima facie obvious. See *In re Kerkhoven* 205 USPQ 1069.

Claims 113-116 and 120-121 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hochrainner et al. (US 6150418, PTO-892 of record) in view of Blondino et al. (US 6004537, PTO-892 of record) or Carling et al. (US 5674860, PTO-892 of record), and further in view of Hardman et al. (Goodman Gilman 's *The Pharmacological Basis of Therapeutics*,1996, page 665, of record) or Leckie et al (*Novel Therapy* Of COPD, abstract, Jan 2000, of record).

The same disclosures of Hochrainner et al. in view Carling et al. (US 5674860) or Blondino et al. have been discussed in the 103(a) rejection set forth above.

Hochrainner et al., Carling et al. and Blodino et al. do not expressly disclose further adding an anticholinergic agent such as ipratropium bromide or tiotropium bromide to the composition therein.

Hardman et al. teaches that ipratropium bromide is an anticholinergic agent useful in treating asthma.

Leckie et al teaches that tiotropium is a known bronchodilator employed in treatment of asthma.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ a third active such as ipratropium bromide or tiotropium bromide in a combination composition along with formoterol and budesonide.

One of ordinary skill in the art would have been motivated to employ a third active such as ipratropium bromide or tiotropium bromide in a combination composition along with formoterol and budesonide because all three actives are known to be useful in treating asthma. Combining two agents which are known to be useful to treat asthma individually into a single composition useful for the very snme purpose is prima facie obvious. See *In re Kerkhoven* 205 USPQ 1069.

In view of the rejections to the pending claims set forth above, no claims are allowed.

Note that applicant's arguments have been considered, but not found persuasive in view of the new ground(s) of rejections made in this office action, and as discussed below.

Applicant argues that "Hochrainer et al. also specifically teaches that its diluted compositions for direct administration are not stable." This argument has been considered, but not found persuasive because Hochrainer et al. teaches a stable formulation containing a solvent mixture of ethanol/water, formoterol in a concentration of about 0.9 to about 1.5 mg/ml adjusted to a pH of about 4.5 to about 5.5. See column 8, claim 22. The concentration of formoterol taught by Hochrainer et al. overlaps with the instantly claimed concentration i.e 5 μg/mL to about 2 mg/mL, and thus the formulation taught by Hochrainer et al. is deemed to have the same stability as instantly claimed.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shobha Kantamneni whose telephone number is 571-272-2930. The examiner can normally be reached on Monday-Friday, 8am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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